Rejections Under 35 U.S.C. §103

Claims 1-10, 12-35, 49 and 51-89 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Kim *et al.* (Cancer Treatment Reports, 1987), or Assil *et al.* (Arch. Ophthamol., 1987), or Bonetti *et al.* (Cancer Chemother. Pharmacol., 1994), or Kim *et al.* (5,723,147) or Sankaram *et al.* (5, 766, 627) in view of Lenke *et al.* (5,948,441). The Examiner has stated that all of the primary references teach processes of making multivesicular liposomes, but that they do not teach cross-flow filtration and making a sterile preparation.

The Examiner further has characterized the secondary reference, Lenke *et al.*, as teaching cross-flow filtration used for selection of large quantities of liposomes of a homogeneous, defined size distribution from a heterogeneously-sized population. The Examiner also has stated that Lenke *et al.* teaches various modes of administration and sterilization. The Examiner then reasons that the use of cross-flow filtration would have been an obvious step in addition to the processes of the primary references because Lenke *et al.* teaches its use in the preparation of liposomes and because one of ordinary skill in the art would realize that such preparations should be sterilized. Applicants respectfully disagree for the following reasons.

The present claims recite two limitations that are not disclosed in any of the primary references. The first limitation relates to forming a composition having "pre-determined, uniform size distribution." The second limitation relates to using cross-flow filtration for "adjusting the concentration of the multivesicular liposomal particle composition." It is not merely cross flow filtration in and of itself that is missing from the primary references, as asserted by the Examiner. Rather, it is the novel use of cross-flow filtration for the particular process steps for which it is applied.

As discussed at length in previous Responses already of record, the primary references each disclose centrifugation as the means for adjusting the final concentration of the multivesicular liposome compositions disclosed therein, and for removing any unwanted buffer and unencapsulated drug. The present invention discloses a novel process whereby cross-flow filtration is used to obtain those objectives, thereby resulting in higher yield and decreased process time. The presently claimed invention is therefore superior over the processes known at the time of the invention. For instance, see Example 13 (page 53, lines 6-7), which demonstrates

an 8.4% improvement in overall yield. Additionally, see Example 15 (page 54, lines 17-19), which demonstrates a reduction in process time from 50 minutes to about 35 minutes (~30%). In industries such as pharmaceutical manufacturing, process improvements in ranges even below 5% can result in significant cost savings. Therefore, the improvements achieved by the claimed process make it remarkably superior to the processes known at the time of the invention.

The claimed process combines the features of "pre-determined, uniform size distribution" and use of cross-flow filtration to achieve these superior effects. This particular application of cross-flow filtration for removal of buffer and unencapsulated drug, and to adjust the concentration of the multivesicular liposomes in the final suspension (as opposed to its use for sterilization), is possible because no size separation of the liposomes is required during this process. The elimination of a process step dedicated to size selection is one factor affecting the increased yield and decreased process time. At the time of the invention, there were no methods for preparing homogeneous suspensions of multivesicular liposomes without a size selection step.

The Examiner has focused on the issue of sterility. Applicants maintain that this issue is not contested. Applicants fully agree that it would be obvious to a person having ordinary skill in the art to prepare sterile compositions for injection. Applicants, however, do not and cannot use filtration as a means for sterilization of the final liposome product due to the massive size of multivesicular liposomes. Therefore, the sterilization process must be carried out as a separate process step apart from the cross-flow filtration.

For reasons of record, the secondary reference, Lenke *et al.*, fails to disclose or suggest the missing elements. The Lenke *et al.* reference discloses that "there remains a difficulty in the art of obtaining a homogeneous population of liposomes." The processes disclosed by Lenke *et al.*, provide a means for treating such undesirable heterogeneous compositions in order to create useful products. In contrast, the present invention discloses a method of producing homogeneous compositions of pre-determined size, requiring no such post-formation size selection.

A person having ordinary skill in the art would not be motivated to employ cross-flow filtration as disclosed by Lenke *et al.*, in the processes disclosed in the primary references. As noted previously, the Lenke *et al.* reference discloses 10 μm as the upper limit of particle size for

which cross-flow filtration is useful (col. 8, lines 53-55). Multivesicular liposomes are generally larger than 10 μm. Presumably, that is the reason that the Lenke *et al.* reference discloses a wide variety of liposomes that may be employed in the disclosed process, but fails to include multivesicular liposomes, which are of relatively massive size.

The Examiner has stated that "The use of cross-flow filtration step in the method of preparation of multivesicular lipid particles of Kim, Assil, Bonetti or Sankaram would have been obvious to one of ordinary skill in the art since Lenke teaches the advantages of using such a step in the preparation of vesicles or liposomes." Applicants strongly disagree. There would have been no motivation to employ cross-flow filtration in the instant process based on the Lenke *et al.* disclosures because the advantages revealed by that reference, *i.e.*, size selection, are irrelevant to the instant process. Thus, cross-flow filtration is used in the Lenke *et al.* process for a different purpose than that of the instant invention, and it is used for compositions comprising particles different from those of the instant invention. There is simply no motivation to combine the process disclosed in the Lenke *et al.* reference with those disclosed in the primary references. In fact, the Lenke *et al.* process teaches away from the present invention by disclosing post-formation size sorting.

Moreover, even if the references are combined, the two limitations missing from the primary references still remain unfulfilled, *i.e.*, formation of a composition having pre-determined uniform size distribution at the time of formation, and use of cross-flow filtration for adjusting the concentration of the multivesicular liposomes in the final suspension.

The Examiner has stated that "With regard to controlling the liposome sizes at the liposome formation step – the examiner points out that it is common knowledge that smaller liposomes will be formed with more mechanical agitation and vice versa." The Examiner has pointed to Example 7 in U.S. Patent No. 5,422,120 in support of his statement. The Examiner has failed to appreciate, however, that such knowledge does not make possible the ability to form liposomes with so small a size distribution range that no post-formation size sorting is required. The process disclosed in the cited patent is essentially the same as those disclosed in the primary references. While the general size of the liposomes may be controlled with energy input, the resulting compositions must still undergo a size-sorting step due to the wide distribution range. Thus, none of the cited references disclose or suggest a process yielding the same results as the

instant invention. For these reasons, Applicants respectfully request reconsideration and removal of this rejection.

Claims 1-10, 12-35, 49 and 51-89 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Kim *et al.* (Cancer Treatment Reports, 1987), or Assil *et al.* (Arch. Ophthamol., 1987), or Bonetti *et al.* (Cancer Chemother. Pharmacol., 1994), or Kim *et al.* (5,723,147) or Sankaram *et al.* (5, 766, 627) in view of Lenke *et al.* (5,948,441) as set forth above, further in view of Kwasiborski *et al.* (6,033,708), Fenske *et al.* (5,837,282), Mehl, Sr. *et al.* (5,885,260), Castor *et al.* (5,776,486), and Moynihan (5,589,189) by themselves or in combination. The Examiner has stated that "One of ordinary skill in the art would be motivated to prepare the multivesicular liposomes in a sterile state because the references of Kwasiborski, Fenske, Mehl, Castor and Moynihan each teach methods that involve the production of sterile liposomes and therefore, a similar sterile production of liposomes is to be expected with instant liposomes also." Applicants respectfully disagree.

Each of the tertiary references teaches methods of sterilizing liposome compositions via filtration techniques. As mentioned previously, multivesicular liposomes are much greater in size than other types of liposomes. Sterilization of the finished product is therefore impossible by filtration, as the liposomes are too large to pass through filters with pore sizes small enough to effect sterilization. Applicants reiterate that the instant method does not employ cross-flow filtration for sterilization purposes. Sterilization is performed either before the liposome formation process, *e.g.,* on the starting materials, or after the liposome formation and concentration adjustment, *e.g.,* just prior to placing the product in vials. Thus, the instant invention uses a process completely different from those disclosed in the tertiary references.

Moreover, none of the tertiary references succeeds in supplying the elements missing from the primary and secondary references, *i.e.,* preparation of compositions having homogeneous size distribution at the time of formation, and using cross-flow filtration to adjust the liposome concentration in the final suspension. For these reasons, Applicants respectfully request reconsideration and removal of this rejection.

Applicants maintain that none of the cited references, either alone or in combination, teach or suggest all of the limitations of the instant invention as presently claimed. Applicants maintain that all pending claims are therefore allowable.

Applicants submit herewith a completed Credit Card Payment Form. Should there be any problems processing the payment, please apply any charges or credits to Deposit Account No. 50-3137.

Respectfully submitted,

Date: 2 SEPT. 2004

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